In-silico Network Pharmacology and Computational Modelling of Bioactive Compounds From Allium Cepa Targeting Downstream Protein Effectors in Diabetes

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Abstract

Network pharmacology is an emerging, cost-effective drug-development approach that uses systems biology and network theory to integrate data and reveal interactions between compounds and their biological targets. Diabetes mellitus is a widespread metabolic disease affecting millions worldwide, while traditional medicine represents knowledge of healing practices inherited across generations and indigenous communities. Allium cepa contains various nutraceutical compounds that give it notable antioxidant, antitumor, antidiabetic, and anti-inflammatory properties. Bioactive compounds of Allium cepa were identified using a phytochemical interactive database. Both the diabetic and bioactive compound target proteins were determined and screened for oral drug bioavailability potential with favorable pharmacokinetic properties. The target proteins underwent protein-protein interaction network analysis, and analyzed using molecular docking analysis. The interaction of kaempferol with PPARG, PPARA and GSK3B possesses − 8.5 kcal/mol, -8.1 kcal/mol, and − 8.0 kcal/mol, respectively. The results obtained showed that kaempferol identified with strong binding affinity with the selected diabetic target proteins and confirmed as the best bioactive compound with an overall interaction profile, antidiabetic property, and good oral drug likeness.

1.0 Background of the Study

Network pharmacology is the latest developmental field, which has promising approaches for a very economical drug development process (Rekha et al., 2023). The network pharmacology approach enhances the provision of a full or a partial understanding of pharmacological data using systems biology and network theory concepts; hence, it is presently being considered as the next model of drug discovery (Zhang et al., 2019). It integrates systematic data to provide interactions between compounds and their targets. Network pharmacology can include processes like screening of active components, enrichment analysis, identification and utilization of disease target databases. It considered an emergent approach in the efficient identification of phytopharmaceuticals to propose hypotheses of mechanisms that can further be validated experimentally (Jiashuo et al., 2022). Moreover, the capability of network pharmacology not only comprises virtual computing and high output rate data analysis but also involves network construction based on the interactions and network topological analysis.

Diabetes mellitus is a prevalent metabolic disorder that has been impacting millions of people globally (Rekha et al., 2023). Diabetes mellitus is a serious metabolic syndrome affecting many worldwide. It is a multigenetic metabolic disease, causing devastating global health challenge, The anti-diabetic drugs currently used are unsatisfactory, presumably due to limitation caused by single target (Wang et al., 2020). Diabetes mellitus implicates a significant risk to human health and ranks as the 9th leading basis of death globally. It is considered as one of the rapidly emerging diseases globally. According to statistics revealed worldwide in 2019, there were approximately 463 million people diagnosed with diabetes and expected to rise to about 693 million by the year 2045.

Diabetes is characterized by hyperglycemia, involving a relative lack of insulin secretion, resistance, or both, i.e., the sugars in food are not used by the body for energy and thus increase the blood glucose level in the body. This happens when the pancreas is not able to produce the required amount of insulin or even when the body is not able to properly process the glucose by resisting insulin (American Diabetes Association, 2010). The two primary types of diabetes are Type 1 and Type 2, each with distinct underlying factors and mechanisms. The level of blood sugar can rise as a result of inadequate secretion of insulin and lower body sensitivity to insulin, resulting

by number of factors, including family history, viral infection, lifestyle and poor dietary habits (Roglic *et al.*, 2016). Type 1 diabetes characterized by a total lack of insulin in the body. Type 2 diabetes is characterizedby insufficient insulin secretion, insulin resistance, and beta cell destruction (Rekha etal., 2023; Sun et al., 2022).

Traditional medicine composed of information and therapeutic methods from the previous generations. In this type of therapy natural herbals or spiritual methods used to treat various deseases (Haux, 2022), emphasizing the significance and historical benefit of traditional medicine in improving health and wellness through ancient practices (Rekha et al., 2023).

Onion (Allium cepa) is a plant in the Liliaceae family that includes beneficial components such as flavonoids, anthocyanins, sulfur-containing compounds, saponins and phenols (Devi, Dhall and Brar, 2025; Nisha *et al.*, 2025). These compounds have been shown scientifically to exhibit therapeutic benefits such as antioxidant, anticancer, antidiabetic and anti-inflammatory properties (Jayaswall et al., 2025). Nutraceuticals are described as "a food or part of a food that provides health benefits beyond its basic nutritional value" (Maria *et al.*, 2024).

This study focuses on investigating anti-diabetic effect of the bioactive compounds from Allium cepa through computational and network pharmacology techniques by interacting with diabetic target proteins.

2.0 Materials and Methods

2.1 Collection and Preparation of Phytocompounds

Seven phytochemical bioactive compounds of Allium cepa were selected from 47 identified phytochemicals using the Phytochemical Interactions Database (PCIDB, 2021) (https://www.genome.jp/dp/pcidp/kna_species). These compounds were characterized using their Simplified Molecular Input Line Entry System (SMILES) collected from the PubChem chemical compounds database, and their drug similarity score was predicted using Lipinski's rule of five model in Swiss ADME (https://www.swissadme.ch).

2.2 Identification of Target Proteins and Construction

The study gathered protein target genes for diabetes mellitus in humans and bioactive compounds of Allium cepa from UniProt and Swiss Target Prediction databases (https://www.swisstargetprediction.ch) as described by Kim et al. (2025). Duplication of predicted target proteins was eliminated during database construction in Microsoft Excel 2019 (Wang et al., 2020). The overlapping genes between the diabetes and bioactive target genes were determined using an online Venn diagram using bioinformatic Venny 2.0 (https://bioinfogp.cnb.csic.es/tools/venny/). A complex information network was constructed based on the interaction of bioactive compounds of Allium cepa and diabetes predicted genes described by Ahmad et al. (2025).

2.3 Gene Set Enrichment Analysis

The study identified biochemical pathways and protein-protein interactions linked to diabetes using ShinyGO 0.85 (https://bioinformatics.sdstate.edu.go/) and String database 12.0V (https://string-db.org/). The pathways significantly associated with the target overlapping genes were identified using the Kyoto Encyclopedia of Genes (KEGG) and Gene Ontology (GO) as described by Kanehisa et al. (2025), and data was transferred to Cytoscape for protein-protein interaction analysis.

2.4 Network construction and Protein-Protein Interaction (PPI)

Based on the data from the enrichment analysis, an interaction network between the proteins was constructed using the Cytoscape 3.10.4 version of the software. Cytoscape software was employed to establish the PPI relationship network and perform topological analysis in order to identify the key genes associated with diabetes mellitus using degree centrality.

2.5 Molecular Docking Studies

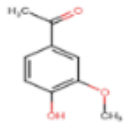
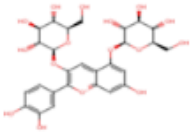
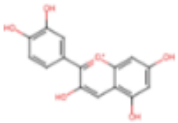
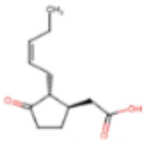
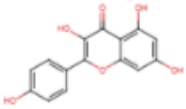
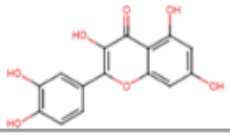
The study analyzed the 3D structures of selected target proteins for diabetes and the seven bioactive ligands of Allium cepa, downloaded from RCSB Protein Data Bank (http://www.rcsb.org/pdb) and PubChem, respectively. The molecular docking studies of the potential therapeutic targets of diabetes selected from Cytoscape and the bioactive ligands were executed using UCSF Chimera 1.18. The docking study was performed initially by preparing the target proteins and the ligands using the Dock Prep tab to remove water molecules and unwanted residue and adding hydrogens and Gasteiger charges using UCSF Chimera 1.18 (Shapovalov and Dunbrack, 2011). The bioactive ligands were docked against the active site of the selected target genes of diabetes. Using the AutoDock Vina tab in Chimera, all default parameters were set, including the grid lines and the docking was run. Molecular interactions such as hydrogen bonding, hydrophobic interaction and electrostatics were examined. The Dock Score feature was used for scoring all the ligands. Analyses have been identified for the best pose. The affinity between the ligands of Allium cepa and the diabetes target shown by the docking score in the current work and the lowest docking energy was determined.

3.0 Results

3.1 Identification of Bioactive Compounds

Fouty seven bioactive phytocompounds of Allium cepa were identified from the phytochemical interaction database PCIDB, among which seven phytocompounds were randomly selected, as presented in Table 1. Their PubChem ID and SMILES were determined from the PubChem database, which was used for the prediction analysis in the SWISS Target Prediction online database.

Table 1: Bioactive Compounds of Allium cepa selected from Phytochemical Interaction Database

Bioactive phytocompounds of *Allium cepa*	PubChem ID	Structure
Allicin	CID_65036	
Apocynin	CID_2214	
Cyanin	CID_441688	
Cyanidin	CID_128861	
Jasmonic acid	CID_5281166	
Kaempferol	CID_5280863	
Quercetin	CID_5280343	

3.2 SWISS ADME Prediction

The pharmacokinetics and drug-likeness of the seven identified phytocompounds of Allium cepa using the online SWISS ADME (https://www.swissadme.ch). Allicin, apocynin, cyanidin, kaempferol, jasmonic acid, and quercetin satisfied the drug-likeness criteria and displayed higher predicted gastrointestinal absorption by passing Lipinski's rule (MW > 500, H-bond donors > 5, H-bond acceptors > 10), unlike cyanin, which showed multiple violations of Lipinski's rule and a low predicted bioavailability score (0.17), indicating poor expected oral bioavailability. Predicted blood-brain barrier permeability was restricted to allicin, jasmonic acid, and apocynin, while kaempferol, cyanin, cyanidin, and quercetin were predicted not to be blood-brain barrier permeant. Concerning the metabolism, quercetin and kaempferol are predicted inhibitors of multiple CYP450 enzymes (notably CYP1A2, CYP3A4 and CYP2D6), while cyanidin shows moderate inhibition limited to CYP1A2. Cyanin, allicin, jasmonic acid and apocynin showed no nosignificant CYP450 inhibition in SwissADME. Toxicity screening indicated no predicted carcinogenicity for any of the seven phytocompounds as presented in Table 2.

Table 2
ADMET Properties of the identified Bioactive Compounds

Compounds	Molecular weight	Water solubility	GI Absorption	BBB Penetration	Bioavailability Score	Lipinski (Drug-like)	Toxicity
Metformin ($C_4H_{11}N_5$)	129.16g/mol	Soluble	High	yes	0.55	Yes	Non-toxic
Cyanin ($C_{27}H_{31}O_{16}^+$)	611.53g/mol	Soluble	Low	No	0.17	No	Non-toxic
Quercetin ($C_{15}H_{10}O_7$)	302.24g/mol	Soluble	High	No	0.55	Yes	Non-toxic
Kaempferol ($C_{15}H_{10}O_6$)	286.24g/mol	Soluble	High	yes	0.55	Yes	Non-toxic
Cyanidin ($C_{15}H_{11}O_6^+$)	287.24g/mol	Soluble	High	No	0.55	Yes	Non-toxic
Allicin ($C_6H_{10}OS_2$)	162.27g/mol	Soluble	High	Yes	0.55	Yes	Non-toxic
Jasmonic acid ($C_{12}H_{18}O_3$)	210.27g/mol	Soluble	High	Yes	0.85	Yes	Non-toxic
Apocynin ($C_9H_{10}O_3$)	166.17g/mol	Soluble	High	Yes	0.55	Yes	Non-toxic

3.3 Target Proteins Identification

The target proteins for diabetes in humans and the selected bioactive compounds of Allium cepa obtained from the UniProt and Swiss Target Prediction databases after eliminating the duplicates are 2159 and 334 genes, respectively. Figure 1 presents the Venn diagram of the intersection between diabetes-related targets and the drug-related target of the Allium cepa, identifying 24 related overlapping genes of the intersection using online bioinformatics Venny tools.

3.4 Gene Enrichment Analysis

The results for the Kyoto Encyclopedia of Genes (KEGG) and Gene Ontology (GO) were presented in Figs. 2, 3 and 4, showing the bar plots and the pathway graph of the overlapping genes.

3.5 Protein-Protein Interaction Network

Table 2 presents the protein-protein interaction network analysis conducted using Cytoscape, identifying the genes with their degree of hierarchy. A total of 23 target genes were analyzed with 23 numbers of nodes, 49 numbers of edges. The average number of neighbors was 5.158, the network diameter was 4, the network radius was 2, the characteristic path length was 1.924, the clustering coefficient was 0.528, the network density was 0.287, the network heterogeneity was 0.766, the network centralization was 0.549, the connected components were 5, and the analysis time taken was 0.005 seconds. From the statistical analysis result, five genes (AKT1, PPARG, PPARA, GSK3B and INSR) were considered for molecular docking analysis, as presented in Fig. 7.

Figures 5 and 6 below present the cytoscape layout of the 23 genes and the five selected genes for docking analysis, respectively.

Table 3
Genes with their degree of Hierarchy after Cytoscape network analysis

SN	GENE NAME	DEGREE
1.	AKT1	14
2.	PPARG	12
3.	PPARA	11
4.	GSK3B	9
5.	INSR	7
6.	NR3C1	7
7.	PIK3R1	7
8.	GCK	6
9.	AKR1B1	5
10.	HDAC5	4
11.	CNR1	3
12.	FABP4	3
13.	RET	3
14.	CDK6	2
15.	RPS6KA3	1
16.	ADRA2A	1
17.	CD38	1
18.	DYRK1B	1
19.	CISD1	1
20.	GPR35	0
21.	AVPR2	0
22.	PTPN22	0
23.	TGM2	0

3.6 Molecular Docking Analysis

The docking results between five selected target proteins (AKT1, PPARA, PPARG, GSK3B and INSR) of diabetes mellitus and the Allium cepa phytochemical compounds (allicin, apocynin, cyanidin, cyanin, kaempferol, jasmonic acid, and quercetin) were presented in Table 3, showing the lower binding energy of the interaction between the

ligands and the respective target proteins. The lower binding energy means affinity is getting higher. The binding energy displays the protein-ligand interaction affinity via an optimized algorithm that functions as an inhibitor. Different hydrophobic groups can contribute significantly to the binding of the target proteins to the hydrophobic cavity.

Table 4
Result for Docking between target proteins of diabetes with ligands from Allium cepa

Target gene for Diabetes	Phytocompound	PubChem ID	Binding Energy (kcal/mol)
AKT1	Allicin	CID_65036	-4.4
	Apocynin	CID_2214	-5.2
	Cyanin	CID_441688	-7.0
	Cyanidin	CID_128861	-6.6
	Jasmonic acid	CID_5281166	-6.6
	Kaempferol	CID_5280863	-6.7
	Quercetin	CID_5280343	-6.8
PPARA	Allicin	CID_65036	-4.5
	Apocynin	CID_2214	-6.1
	Cyanin	CID_441688	-6.9
	Cyanidin	CID_128861	-6.7
	Jasmonic acid	CID_5281166	-4.5
	Kaempferol	CID_5280863	-8.1
	Quercetin	CID_5280343	-6.8
PPARG	Allicin	CID_65036	-3.8
	Apocynin	CID_2214	-6.1
	Cyanin	CID_441688	-8.3
	Cyanidin	CID_128861	-7.7
	Jasmonic acid	CID_5281166	-5.5
	Kaempferol	CID_5280863	-8.5
	Quercetin	CID_5280343	-7.9
GSK3B	Allicin	CID_65036	-3.8
	Apocynin	CID_2214	-5.5
	Cyanin	CID_441688	-9.2
	Cyanidin	CID_128861	-7.4
	Jasmonic acid	CID_5281166	-5.6
	Kaempferol	CID_5280863	-8.0
	Quercetin	CID_5280343	-8.3
INSR	Allicin	CID_65036	-3.6

Target gene for Diabetes	Phytocompound	PubChem ID	Binding Energy (kcal/mol)
	Apocynin	CID_2214	-5.2
	Cyanin	CID_441688	-8.7
	Cyanidin	CID_128861	-8.3
	Jasmonic acid	CID_5281166	-5.5
	Kaempferol	CID_5280863	-7.6
	Quercetin	CID_5280343	-7.8

Figure 8 present the molecular docking results showing the interaction between the selected diabetic target proteins (PPARA, PPARG, GSK3B) and Kaempferol (ligand like compound) identified from Allium cepa.

4.0 Discussion

The randomly selected bioactive compounds identified from PCID were presented in Table 1 with their respective structures downloaded from PubChem, and their pharmacokinetics and drug likeness (ADMET) were observed and reported in Table 2. All the bioactive compounds pass the rule of five, making them pass Lipinski's rule except Cyanin, with a molecular weight of > 500 g/mol (611.53 g/mol). The rule of five (Ro5) predicts the bioavailability of the bioactive compounds. The ADMET properties of the bioactive compounds were compared with a standard diabetic drug (metformin), and many pharmacokinetic properties were in common, this confirms the anti-diabetic properties of the bioactive compounds identified from Allium cepa. This research work was in accordance with the work done by many researchers proving the antidiabetic properties of allicin (Li et al., 2022), apocynin (Sánchez-Duarte et al., 2025), cyanidin (Singh et al., 2022; Ye et al., 2024), kaempferol (Yang et al., 2022), and quercetin (Slimestad et al., 2007). Yan et al. (2023) reported that the antidiabetic mechanism of action involves modulation of multiple molecular targets and signaling pathways associated with the insulin resistance and the pathogenesis of diabetes and this enhances insulin sensitivity and reduces blood glucose level.

In this study, analysis of the therapeutic target PPI network identified AKT1, PPARG, PPARA, GSK3B and INSR as the key core targets associated with Allium cepa's pharmacological activity. These genes have been reported to be involved in the pathological processes of Type 2-diabetes-AKT1 (Camaya et al., 2022, Miao et al., 2022, Zhang et al., 2019), PPARG (Cooreman et al., 2024, Frkic et al., 2021), PPARA (Joly et al., 2009), GSK3B (Teli *et al.*, 2023), and INSR (Chen et al., 2019). The result of the GO and KEGG enrichment analysis showed that active components of Allium cepa can regulate various biological processes, cellular component, molecular function, and pathways to treat Diabetes. The genes contribute to the molecular mechanisms fundamental to sensitivity of insulin and control of metabolism, hence are implicated in the advancement or prevention of metabolic syndrome like type 2 diabetes. Hong *et al.* (2013) affirmed that glucose homeostasis is essential, and that any disruption in this balance may result in metabolic disorder manifesting as type 2 diabetes mellitus. The response to insulin is an indication that the identified genes are involved actively in the insulin signaling cascade and its consequential effects on cell metabolism. The Cellular component category of the analysis showed that the proteins encoded by the identified genes are mostly situated in the mitochondrion, Axon, perinuclear region of the cytoplasm, and Receptor complex. Enrichment in the mitochondrion is an indication that these genes are associated with redox balance and energy metabolism which are usually compromised in Type 2 diabetes mellitus (Lowell & Shulman, 2005). The identified bioactive compound in Allium cepa have been reported to increase mitochondrial

biogenesis, reduce reactive oxygen species (Ho et al., 2022), enhance insulin production and glucose metabolism (Mijgar & Deokate, 2023, Ansari et al., 2022), hence, improving glucose utilization necessary in the management of Type 2 diabetes mellitus. The axon enrichment suggests involvement of the central nervous system (CNS) and neurons. The CNS functions in the regulation of insulin secretion and sensitivity (Güemes and Georgiou, 2018). Central Nervous system control of glucose is a drug target for diabetes mellitus (Mirzadeh et al., 2022). From the KEGG pathway, the drug targets of Allium cepa against diabetes mellitus were mainly linked to insulin signaling pathway, diabetes mellitus, and insulin resistance. The major highlighted nodes like P13K, IRS1/2, PPAR, AKT, AMPK, MAPK/JNK, and glycogen metabolizing enzymes were enriched prominently. This indicates defective glycogen synthesis, impaired GLUT4 translocation, improved inflammatory signaling and gluconeogenesis as presented in Fig. 4.

The docking analysis reported high binding energy (-9.2 kcal/mol) at the interaction between the diabetic target protein (GSK3B) and ligand (Cyanin) identified from Allium cepa, followed by the interaction of Cyanin with INSR and PPARG with − 8.7 kcal/mol and − 8.3 kcal/mol, respectively, as presented in Table 4. The drug-likeness and pharmacokinetic properties of the phytocompound (cyanin) do not pass Lipinski's rule (rule of five) with low gastrointestinal absorption; therefore, it cannot be predicted as a drug. The interaction of GSK3B with quercetin and INSR with cyanidin possesses the same binding energy of -8.3 kcal/mol. The interaction of kaempferol with PPARG, PPARA and GSK3B possesses − 8.5 kcal/mol, -8.1 kcal/mol, and − 8.0 kcal/mol, respectively. This study revealed that kaempferol fits perfectly into the hydrophobic pocket of each receptor with strong binding interactions with the three diabetic target proteins (PPARA, PPARG, GSK3B) with strong binding affinity. According to the drug-likeness and pharmacokinetics properties presented in Table 2, kaempferol is identified as the best phytocompound to be confirmed as the drug with antidiabetic property.

5.0 Conclusion

In this study, phytocompounds were identified from Allium cepa and screened for oral drug bioavailability potential with favorable pharmacokinetic properties. The results obtained showed that kaempferol, quercetin, and cyanin were identified as having a strong binding affinity with the selected diabetic target proteins (INSR, PPARA, PPARG, DSK3B), and kaempferol was confirmed as the best bioactive compound with an overall interaction profile, antidiabetic property, and good oral likeness.

Declarations

There is no any Ethical approval and consent applicable to this research work

Consent for publication also not applicable

The authors declare no any conflict of interest

This research work received no external funding

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request

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Author Contribution

Aliyu and Ani Conceptualized the study, designed the research framework, performed molecular docking and interpretation of results, and drafted the initial manuscripts.Shamsudeen, Al-amin, Mustafa, Michael and James contributed to target prediction, network pharmacology and pathways enrichment analysisChika, Onwu, Mayowa, and Alexander provided the overall supervision, critically reviewed the manuscript, contributed to the interpretation of pharmacological relevance, and approved the final version for submission.

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Figures

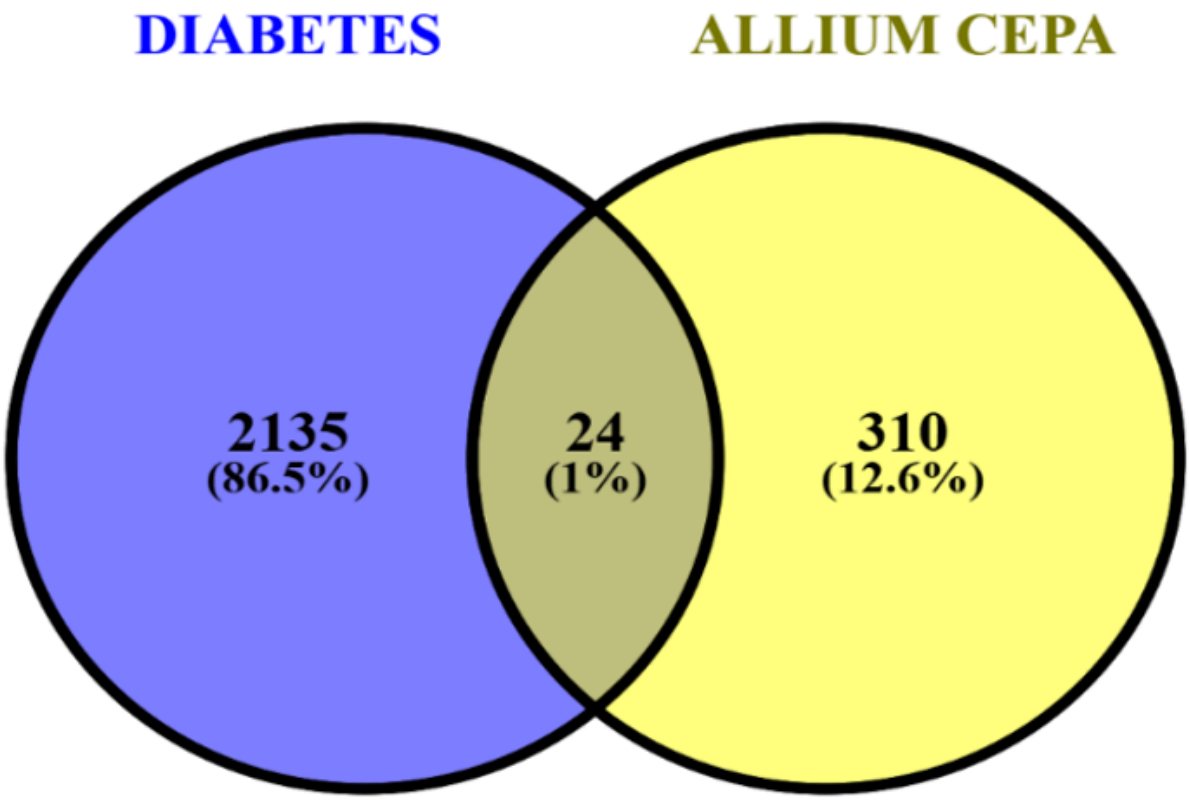

Figure 1

Venn diagram of the intersection of target genes of diabetes and allium cepa phytocompounds identifying the overlapping genes

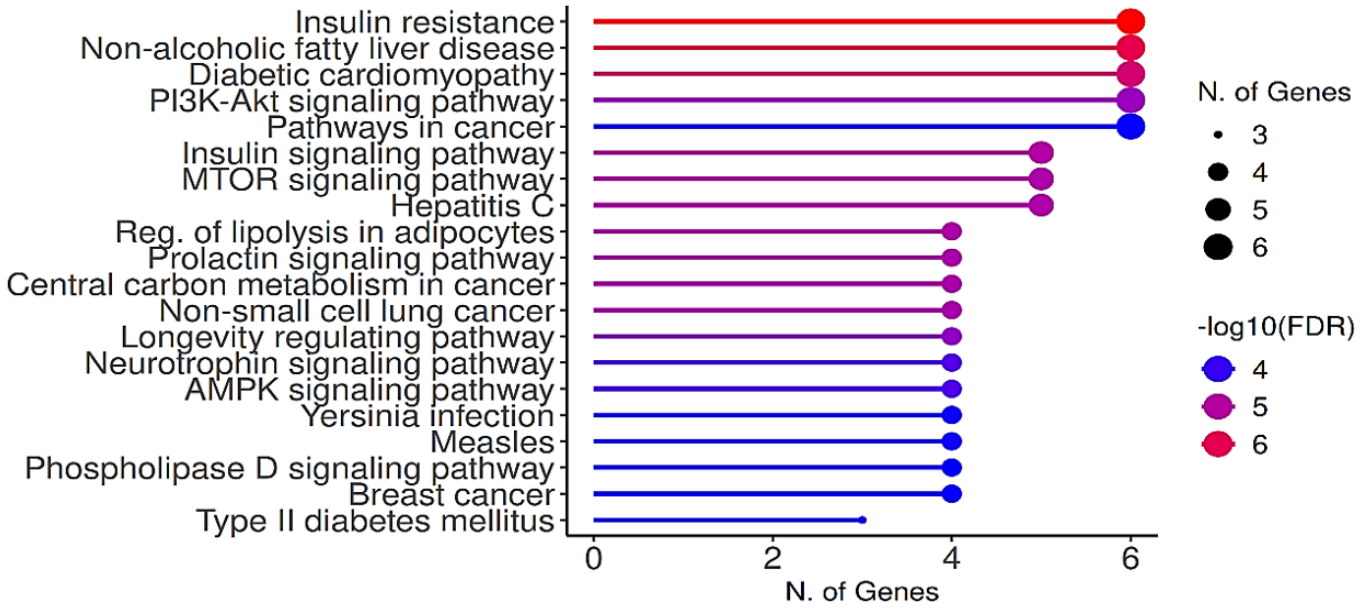

Figure 2

Bar Plot of KEGG of the overlapping genes identified

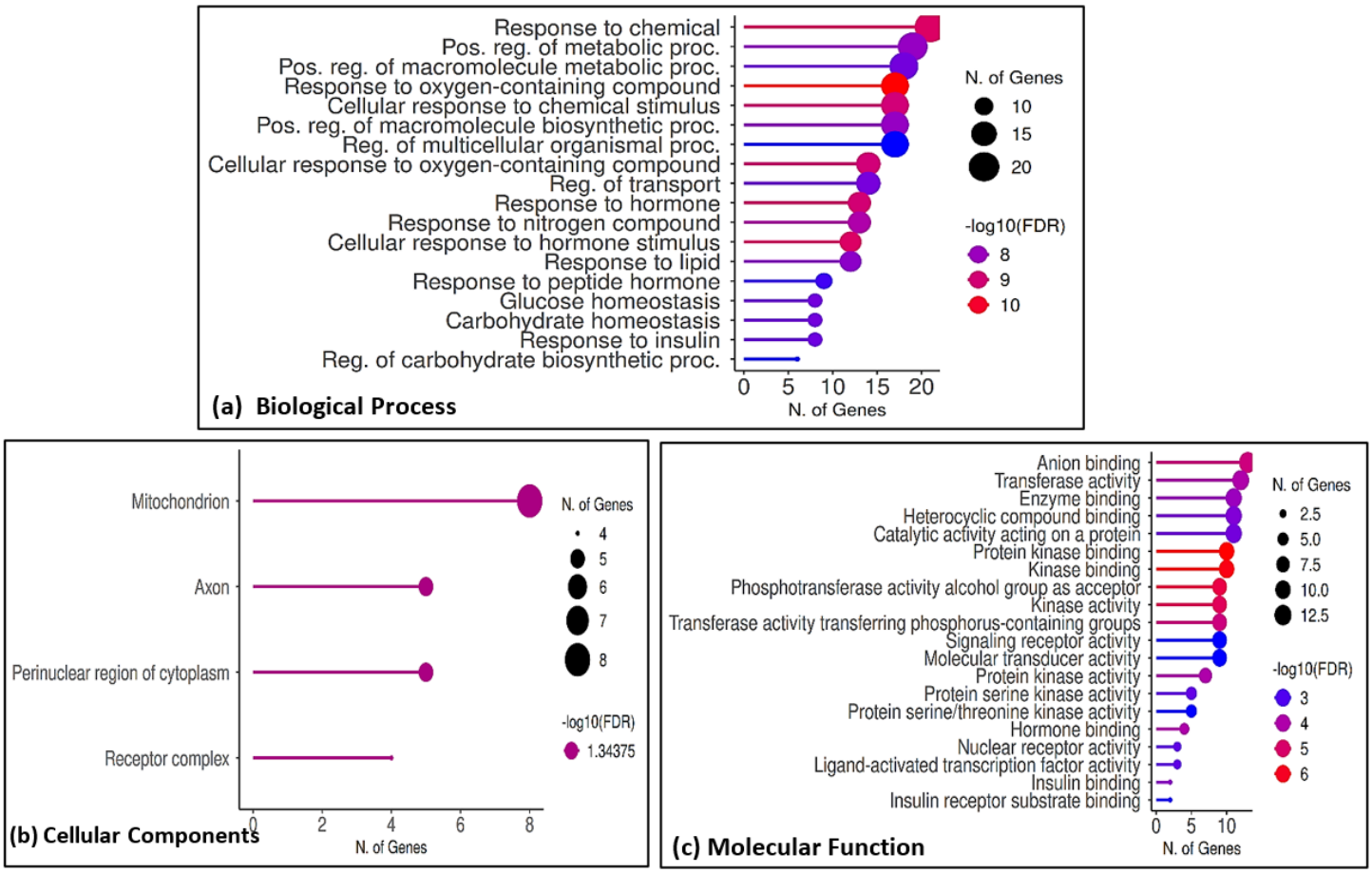

Figure 3

Bar Plot of KEGG of the overlapping genes identified

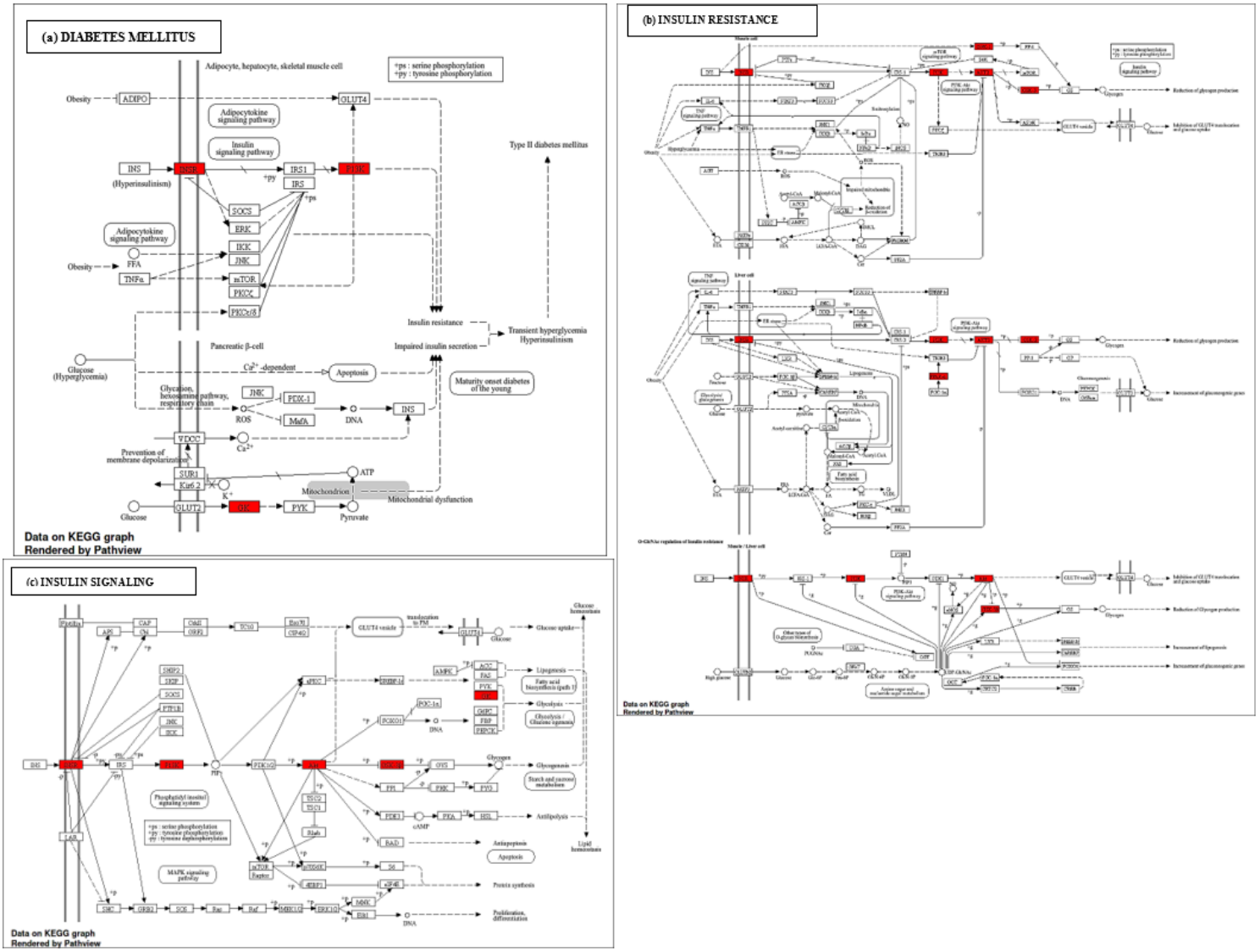

Figure 4

KEGG Graph Pathways of the Overlapping Genes

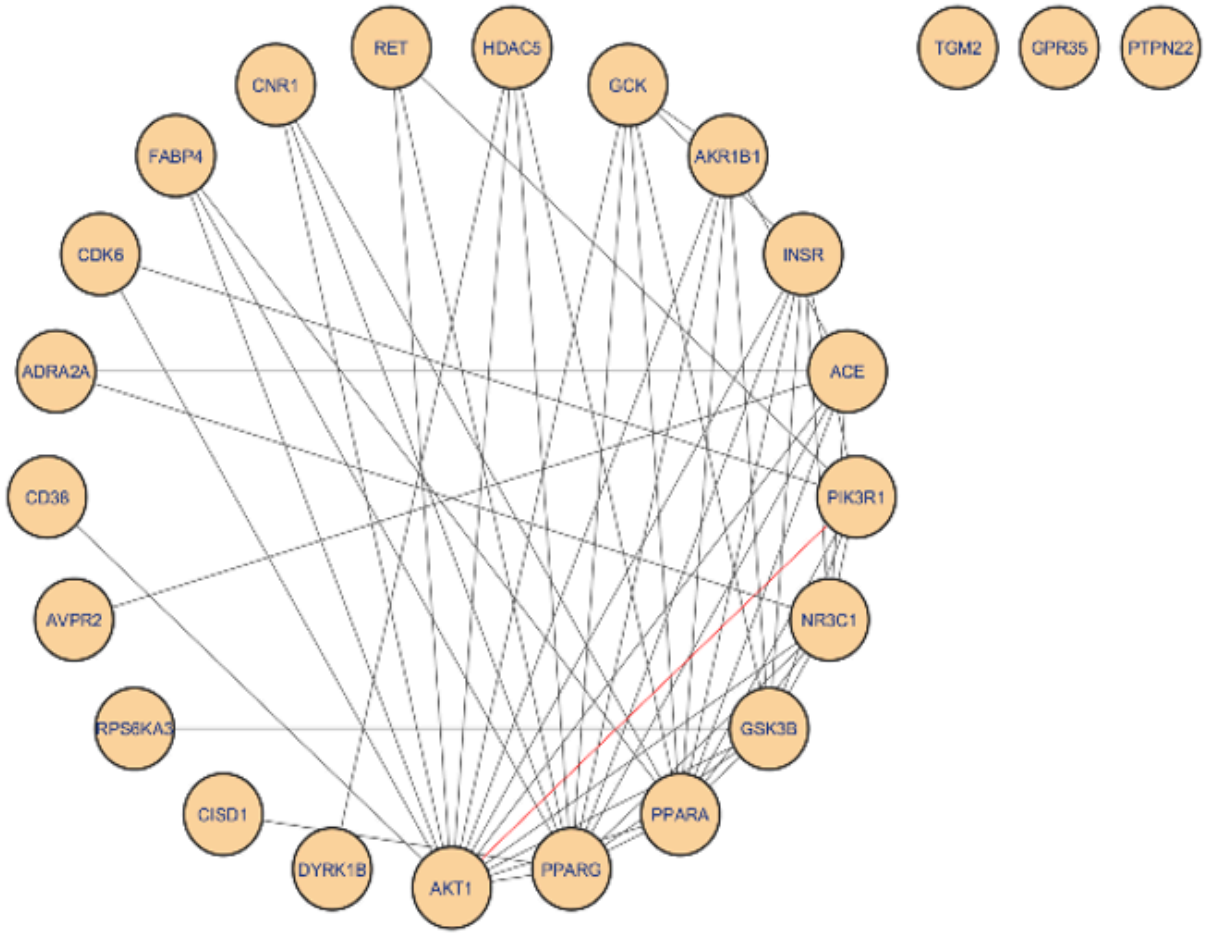

Figure 5

Circular Layout of 23 protein-protein interaction of Overlapping Target genes in cytoscape

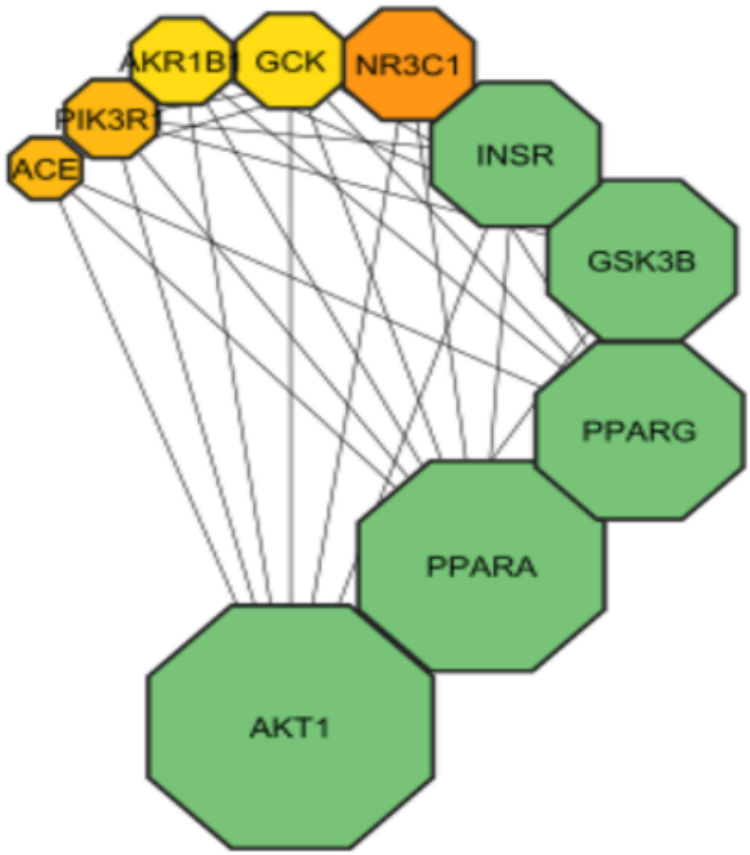

Figure 6

Protein-Protein interaction of the most Hierarchical gene after Network Analysis in Cytoscape

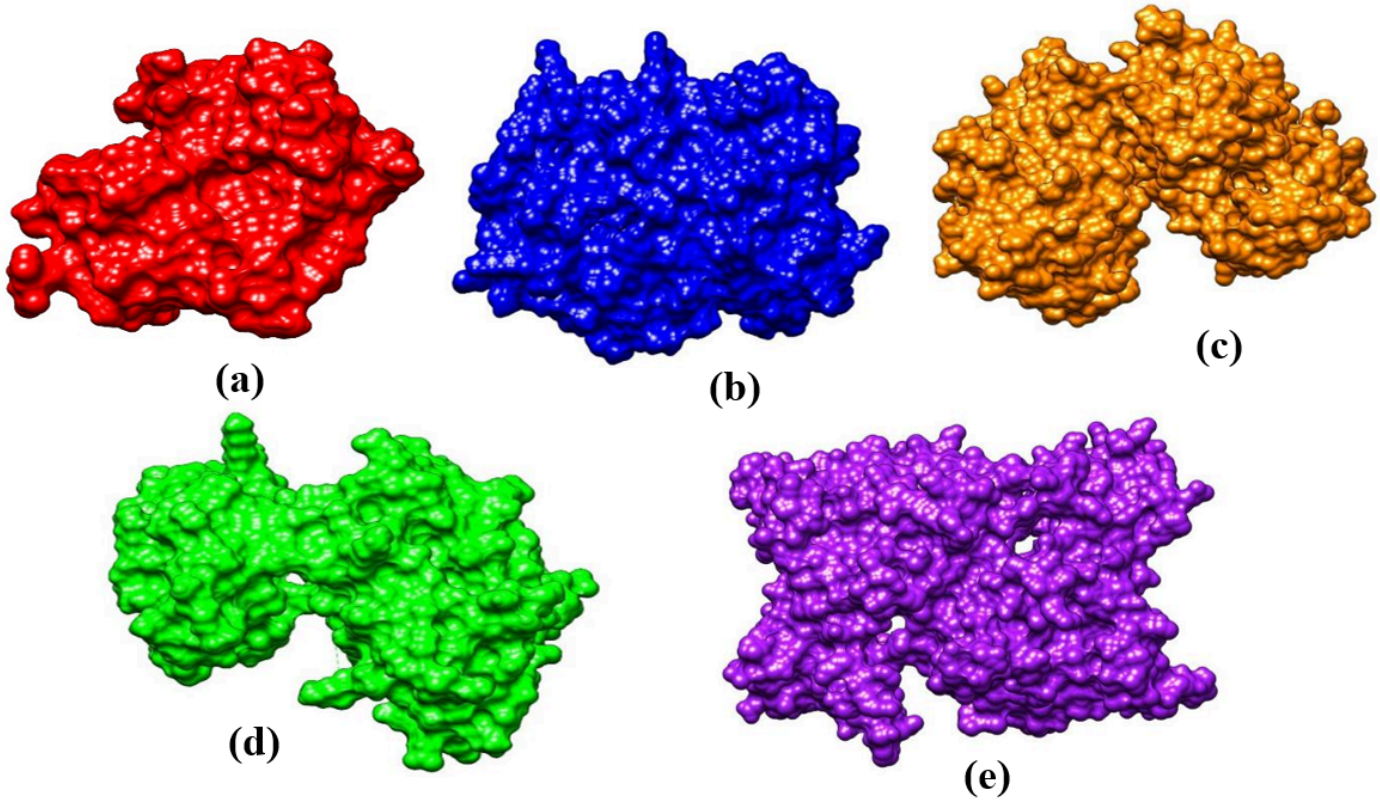

Figure 7

3D representation of (a) AKT1 Gene (PDB ID: 8R5K), (b) PPARA (PDB ID: 8RCE), (c) PPARG (PDB ID: 8WFE) (d) INSR (PDB ID: 3EKK) (e) GSK3B (PDB ID: 1I09)

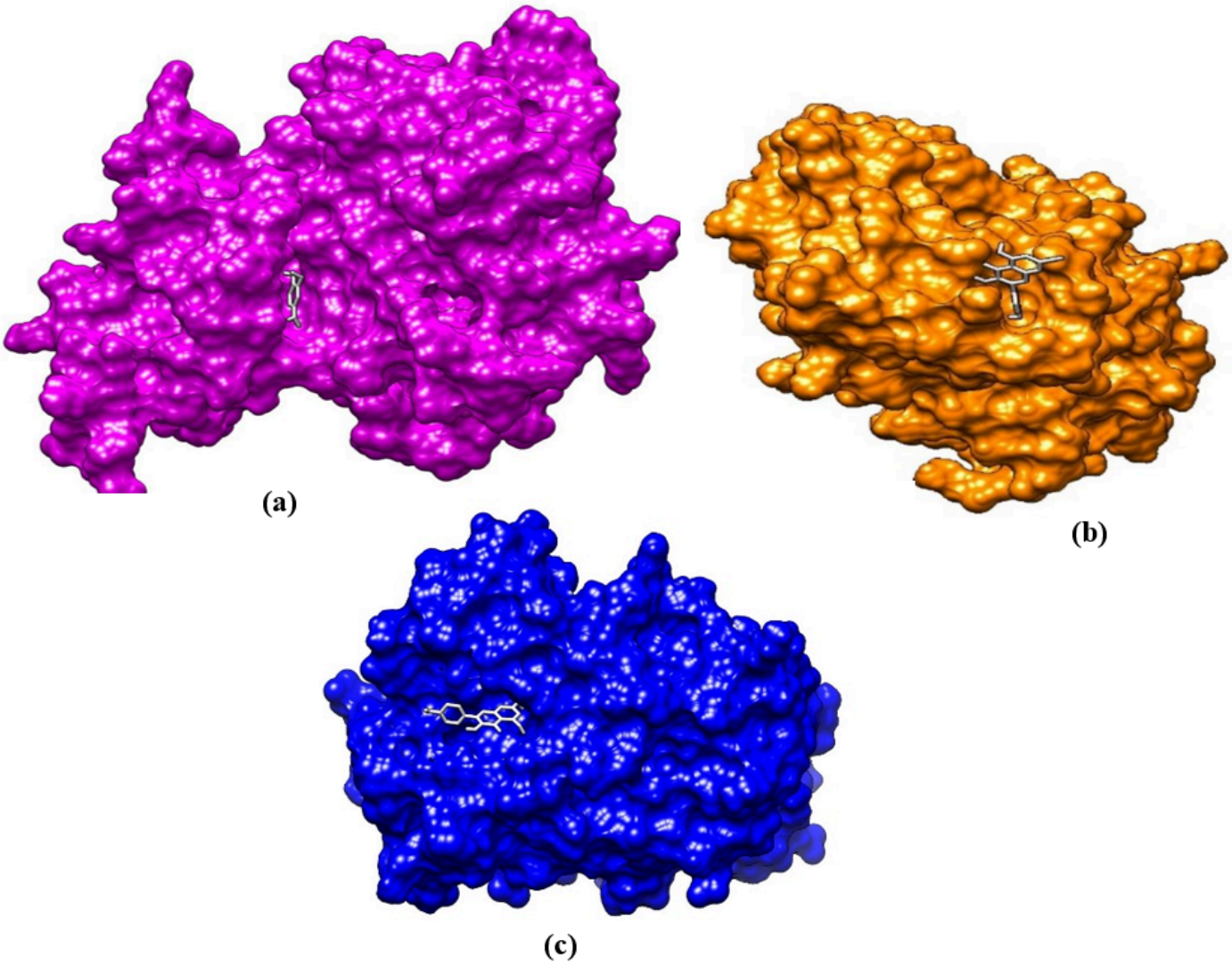

Figure 8

Molecular Docking Result Identifying (a) Kaempferol VS GSK3B, (b) Kaempferol VS PPARG (c) Kaempferol VS PPARA